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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,016	09/10/2001	Janet A. Warrington	03848-00093	9580

28315 7590 06/24/2004

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EXAMINER

JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

3-14

Office Action Summary	Application No.	Applicant(s)	
	09/950,016	WARRINGTON ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 February 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,7-14 and 18-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,7-14 and 18-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

FINAL ACTION

1. This action is responsive to the Amendment and Response filed February 23, 2004. Claims 1-2, 7, 11-14, 18, and 22-23 have been amended, and claims 3-6, 15-17, and 26-36 have been canceled. Claims 1-2, 7-14, and 18-25 are now pending and under consideration. Applicants' arguments have been thoroughly considered, but are not persuasive for the reasons that follow. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. Regarding Applicants' amendment to the paragraph starting on page 19, line 19, the amendment appears to contain a typographical error. Particularly, the capitalized version of the trademark SUPERScript is marked by strike-through (indicating deletion, although the text is new), while the prior recitation of "Superscript" is underlined (although it is not new). Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 1-2, 7-14, and 18-25 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement, for reasons stated in the Office action of July 30, 2003. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

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It is first noted that Applicants' amendments have overcome the instant rejection in part. Specifically, the claims as amended are now limited to human subjects. However, the claims as written still encompass methods in which any gene "associated with oral cancer" is detected, and claims 22-25 encompass methods of "monitoring the progression" of oral cancer in which marker expression levels at different time points are detected in order to monitor progression.

The response traverses the rejection on the following grounds. The response argues that the specification provides enabling working examples, including teachings of "how to prepare nucleic acid samples...including use of a technique of separating normal cells from tumor cells from the same solid tumor sight," of "the analysis of nucleic acid samples using microarrays," and of "how to analyze raw data obtained by microarray experimentation" using various software programs. The response urges that "Applicants teach that the expression of nucleic acids associated with oral cancer may easily be identified by comparing gene expression in normal cells vs. gene expression in tumor cells wherein the cells are obtained from the same individual," and that "although one of skill would have to compare the two cell types and determine gene expression levels, such experimentation would be routine" and not undue.

These arguments have been thoroughly considered but are not persuasive. It is acknowledged that methods of nucleic acid sample preparation, microarray analysis, and software data analysis, as well as methods of comparing gene expression in different cell populations, may be readily practiced

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by those of skill in the art. However, the instant claims are not merely drawn to such well known methods and research tools. Rather, claims 1-2 encompass identifying any gene that hybridizes differently in any way to different types of probe arrays as being "associated with oral cancer" (claim 1) or "differentially expressed" (claim 2). While it is clear from the teachings of Applicants' specification that a particular subset of genes are in fact differentially expressed in oral cancer tissues as compared to normal oral tissue, the claims as written encompass the identification of virtually any gene as being "associated with oral cancer" and/or differentially expressed. Further, with regard to claim 7 and claims dependent therefrom, while it is clear from the teachings of the specification that detection of the expression levels of certain genes would aid in oral cancer diagnosis, this would not be the case for any gene "associated with oral cancer" as defined by Applicants (i.e., for virtually any gene). Further, it is noted that Applicants' response does not traverse the rejection with regard to enablement of methods of monitoring oral cancer progression; thus, such methods lack enablement for the reasons of record.

As Applicants' arguments are not persuasive, this rejection is maintained.

**THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED
BY APPLICANTS' AMENDMENTS:**

5. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 1 is indefinite over the recitation of the phrase “wherein a gene that hybridizes differently is associated with oral cancer.” It is noted that the method steps of claim 1 refer to hybridization of probe arrays with populations of nucleic acids, but never mention or refer to hybridization of a gene or genes.

Accordingly, it is unclear as to how the practice of the recited method steps could or would result in identifying a “gene” that “hybridizes differently” and is “associated with oral cancer.” Clarification is required.

Claim 2 is indefinite over the recitation of the limitation “the binding of the second array of probes” because there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

6. In view of Applicants’ amendments to claims 1-2, such that the claims now require first and second populations of nucleic acids from the same human subject, the rejection of claims 1-2 under 35 U.S.C. 102(b) as being clearly anticipated by Chang et al (Oncogene 16(15):1921-1930 [4/1998]) is withdrawn.

Claim Rejections - 35 USC § 103

7. Claims 1-2, 7-9, 11-14, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al (U.S. Patent No. 6,171,798 [01/09/2001; effective filing date 3/27/1998]) in view of Chang et al (Oncogene 16(15):1921-1930 [4/1998]), for the reasons stated below and in the Office action of July 30, 2003. **It is noted that Applicants’ amendments to the claims necessitated the inclusion of claims 1-2 in this rejection.**

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It is first noted that Applicants have amended claims 1-2 so as to require first and second populations of nucleic acids from the same human subject. Similarly, Applicants have amended claim 7 so as to require test and control samples from the same human subject. As Levine et al disclose both test and matched control tissue samples from a human subject, Levine et al (in addition to the teachings discussed in the prior Office action) teach this new claim limitation (see, e.g., col 4, lines 53-65 of Levine et al).

The response traverses the rejection on the following grounds. The response states that "The Examiner admits that Levine et al. does not specifically teach detection of oral cancer, or teach the use in their method of cells obtained from oral tissue," and further that "Levine et al. does not teach or suggest comparing expression of a marker in a test sample and a control sample from the same subject." The response further argues that "Chang et al. fails to cure the deficiencies of the primary reference for at least the reasons set forth above," and that "neither reference recognizes the benefit of comparing samples derived from the same individual."

These arguments have been thoroughly considered but are not persuasive. First, it is again acknowledged that the Levine et al reference does not teach detection of oral cancer or the use of oral tissues or cells; it is for this reason that the Chang et al reference was cited. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375

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(Fed. Cir. 1986). Additionally, the Levine et al reference does teach the use of test and matched control tissue samples from the same patient (see, e.g., col 4, lines 53-65 of Levine et al). Thus, it is unnecessary for Chang et al to provide this teaching, and with further regard to the Chang et al reference, the response does not indicate any other specific reasons why the reference is believed by Applicants to “fail to cure the deficiencies” of Levine et al. Accordingly, Applicants’ arguments are not persuasive.

The combined references of Levine et al and Chang et al suggest all the limitations of present claims 1-2, 7-9, 11-14, and 18-21, and therefore this rejection is maintained.

8. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al in view of Chang et al, as applied to claims 1-2, 7-9, 11-14, and 18-21, above, and further in view of Ts’o et al (U.S. Patent No. 5,962,237 [10/05/1999; filed 04/02/1997]), for the reasons stated below and in the Office action of July 30, 2003.

As discussed in paragraph 7, above, it is noted that Applicants have amended claim 7 (from which claim 10 depends) so as to require test and control samples from the same human subject. As Levine et al disclose both test and matched control tissue samples from a human subject, Levine et al (in addition to the teachings discussed in the prior Office action) teach this new claim limitation (see, e.g., col 4, lines 53-65 of Levine et al).

The response traverses the rejection on the grounds that the combined teachings of the Levine et al and Chang et al references do not render the

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invention obvious, for the reasons discussed in paragraph 7, above. Accordingly, the response to those arguments applies equally herein. The response further argues that "Ts'o et al. does not teach or suggest comparing expression of a marker in a test sample and a control sample from the same subject." However, the Ts'o et al reference was not cited for such teachings, but for its teaching that cancer cells present in the blood are indicative of cancer metastasis, and its disclosure of methods for enriching such cells so as to facilitate detection of cancer metastasis. Accordingly, Applicants' arguments are not persuasive.

The combined references of Levine et al, Chang et al, and Ts'o et al suggest all the limitations of present claim 10, and therefore this rejection is maintained.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

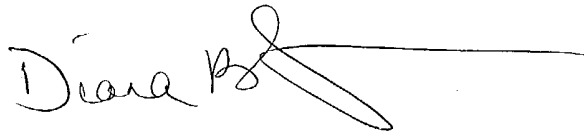
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the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read "Diana B. Johannsen", followed by a long horizontal line extending to the right.

Diana B. Johannsen
Primary Examiner
June 23, 2004